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Diabetes Mellitus – An overview

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Diabetes mellitus, or simply diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria, (frequent urination), polydypsia (increased thirst), and polyphagia (increased hunger).

There are three main types of diabetes mellitus (DM).

- Type 1 DM results from the body's failure to produce insulin, and currently requires the person to inject insulin or wear an insulin pump. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes".
- Type 2 DM results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. This form was previously referred to as non-insulin-dependent diabetes mellitus (NIDDM) or "adult-onset diabetes".
- The third main form, gestational diabetes, occurs when pregnant women without a previous diagnosis of diabetes develop a high blood glucose level. It may precede development of type 2 DM.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic-fibrosis related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

Untreated, diabetes can cause many complications. Acute complications include and nonketotic hyperosmoral coma. Serious long-term complications include cardiovascular disease, chronic renal failure, and diabetic retinopathy (retinal damage). Adequate treatment of diabetes is thus important, as well as blood pressure control and lifestyle factors such as stopping smoking and maintaining a healthy body weight.

Keyword: Diabetes Mellitus, Insulin, Pancreas.

1. Introduction

Diabetes mellitus (DM) is a group of metabolic disorder in which a person has high blood sugar either because the body does not produce enough insulin or cells do not respond to the insulin that is produced. It is a lifelong disease. The prevalence of diabetics is rapidly rising all over the world at an alarming rate.

2. Symptoms:

- Frequent urination
- Increased hunger
- Fatigue and weakness
- Increased thirst
- Blurred vision
- Nausea and vomiting
- Sudden weight loss or gain
- Skin infections

- Chronic itching
- Poor healing of wounds

Frequent headache, dizziness, nervousness.

Table 1: Glucose measurements

The following parameters are taken into consideration:	
Preprandial plasma glucose (before a meal)	70–130 mg/dl (3.9–7.2 mmol/l)
Postprandial plasma glucose (after a meal)*	140-199 mg/dL (7.8-11.1 mmol/l)
HDL	>40 mg/dl (>1.1 mmol/l)
*Postprandial glucose may be targeted if A_{1c} goals are not met despite reaching preprandial glucose goals.	

3. Diagnosis

The American Diabetes Association suggests the following targets for most non pregnant adults with diabetes. More or less stringent glycaemic goals may be appropriate for each individual[1].

The fasting and postprandial glucose levels do not measure the same physiological process and do not identify the same individual as having diabetes.

A fasting glucose reflects hepatic glucose production which depends on insulin secreting capacity of the pancreas. The post prandial glucose reflects uptake of glucose in peripheral tissues (muscles and fat) and depends on insulin sensitivity of these tissues.

The ADA 2011 recommends the use of HbA_{1c} determinations to monitor the glycaemic control in diabetic patients.

4. Types of Diabetes Mellitus

1. Type 1 diabetes mellitus (IDDM) (T1DM)
2. Type 2 Diabetes mellitus (NIDDM) (T2DM)
3. Gestational diabetes

4.1 Type 1 Diabetes Mellitus:

The term T1DM has universally replaced former terms including childhood onset diabetes, juvenile diabetes, and insulin dependent diabetes mellitus. It is characterized by loss of insulin produced by β-cells of islets of langerhans of pancreas. It should be noted that there is no known preventive measures that can be taken against T1DM. The principal treatment of T1DM, even from the earliest stage is exogenous insulin.

4.2 Type 2 Diabetes Mellitus:

It is due to the combination of defective insulin secretion and insulin resistance or reduced insulin sensitivity (defective responsiveness of tissues to insulin), which almost certainly involves the insulin receptor in the cell membrane.

The etiology of the condition bears strong genetic heredity and obesity. Hence, insulin therapy may not prove to be quite effective [2].

4.3 Gestational Diabetes Mellitus:

Gestational diabetes involves a combination of in adequate insulin secretion and responsiveness resembling type2 diabetes mellitus in several aspects. It develops during pregnancy and may continue or disappear after delivery. Even though it may be transient, gestational diabetes may damage the health of fetus or mother[2].

5. Risk Factors:

5.1 Risk Factors of T1DM:

With T1DM, which starts in childhood, the pancreas stops producing insulin. Insulin is a hormone the body needs for using the energy from carbohydrates found in food[1]. The primary risk factors for T1DM are,

- **Genetics and family history**- The American Diabetes Association recommends that anyone with a first-degree relative with T1DM is prone to get T1DM.
- **Diseases of the pancreas**- Injury or diseases of the pancreas can inhibit its ability to produce insulin and lead to T1DM.

- **Infections or illness** can damage the pancreas and cause T1DM.
- E.g.: cow's milk or viral, dietary or other environmental exposure that initiates auto immune process.

6. Pathophysiology of T1DM:

6.1 Pathophysiology of Diabetes Melletes

T1DM is characterized by an absolute deficiency of insulin. This is the result of an immune mediated destruction of pancreatic β cells[11]. The autoimmune process is mediated by macrophages and with T- lymphocytes with circulating auto antibodies to various β cell antigens. The most commonly detected antibodies associated with T1DM are the islet cell antibodies, insulin antibodies, antibodies directed glutamic with decarboxylase, Insulin antibodies against islet tyrosine phosphatase. More than 90% of newly diagnosed persons with T1DM have one or another of these antibodies as will 3.5-4% of unaffected first degree relatives.

7. Treatment:

Insulin that comprises of a 21 residue a chain is strategically linked with two disulphide bonds ultimately to a 30- residue B chain. It is the mainstay of treatment of T1DM patients, administered exogenously.

8. Insulin:

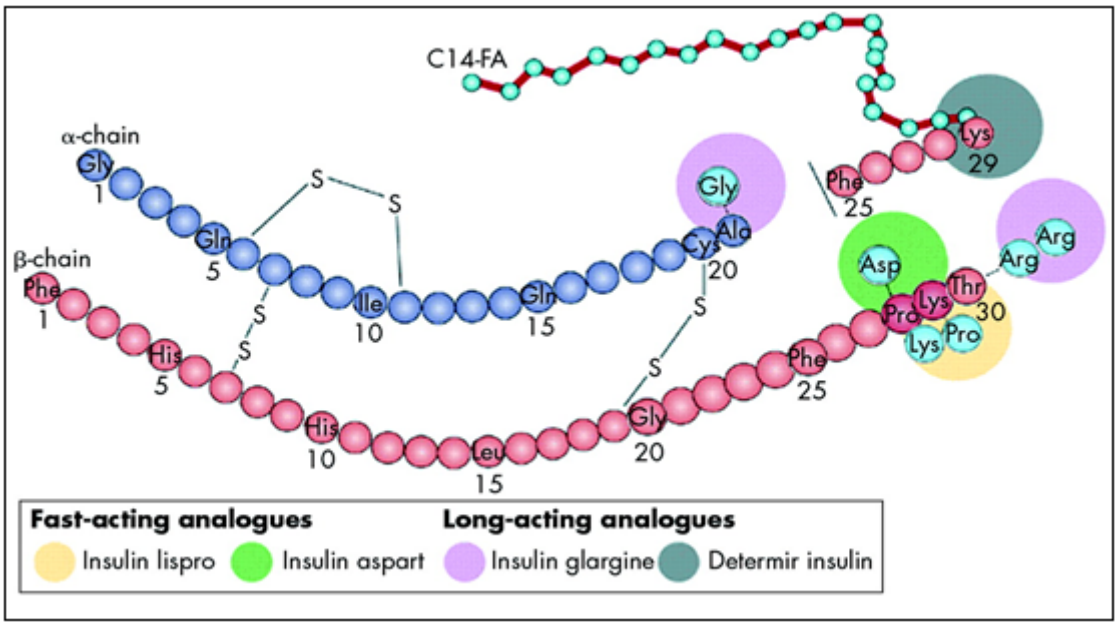

Fig 1: Structure of insulin and the site of actions of insulin analogues

8. Sources: The conventional, commercial preparations are prepared from beef and pork pancreas[4]. Currently it is prepared by rDNA technology. This includes,

8.1 Human insulin's

Human insulin's (having the same amino acid sequence as human insulin) is produced by recombinant DNA technology in *E. coli* in yeast or by enzymatic modification of porcine insulin. Human insulin is more water soluble as well as hydrophobic than porcine or bovine insulin. They are specially indicated in the following situations.

1. Insulin resistance – especially when due to large amounts of insulin binding antibodies.
2. Allergy to conventional preparations.
3. Injection site- lipodistrophy
4. Short-term use of insulin in diabetics who are otherwise stabilized on diet and exercise with/without oral hypoglycemic.
5. during pregnancy

9. Formulations of Insulin

9.1 Regular (soluble) insulin:

It is a buffered solution of unmodified insulin stabilized by a small amount of zinc. Is injected subcutaneously (sc) just before a meal.

9.2 Lente insulin (insulin zinc suspension)

Two types of insulin-zinc suspensions have been produced the one with large particles is crystalline and practically insoluble in water (ultra lente or extended insulin zinc suspension). It is long-acting. The other one has smaller particles and is amorphous (semi-lente or prompt insulin zinc suspension), is short-acting. Thus their 70:30 ratio mixtures are called lente insulin and are intermediate acting.

9.3 Isophane (neutral protamine hagedorn or NPH insulin)

Protamine is a complex in insulin molecule to form a neutral protamine hagedorn at normal pH. On subcutaneous injection, the complex dissociates slowly to yield an intermediate duration of action.

9.4 Protamine zinc insulin

It contains excess of protamine, so that the complexed insulin is released more slowly at the site of sc injection and a long acting preparation results.

9.5 Insulin analogues:

Using rDNA technology, analogues of insulin have been produced with modified pharmacokinetics on sc injection but similar pharmacodynamics effects. Greater stability and consistency are the other advantages.

9.6 Insulin lispro:

Produced by reversing proline and lysine at the carboxy terminus. It provides a better control of meal – time glycaemia and a lower incidence of late post prandial hypoglycemia.

9.7 Insulin asparte:

The proline at B28 of human insulin is replaced by aspartic acid. This change reduces the tendency of self-aggregation, and a time action profile similar to insulin lispro is obtained.

9.8 Insulin glargine: This is a long acting bio synthetic Insulin with greater stability.

10. Risk Factors of T2DM:

- **Obesity or being overweight**. Diabetes is directly associated with obesity[1].
- The most-used measure for obesity is BMI, which stands for body mass index. BMI is a ratio, and can be determined using standard tables of height and weight. A BMI of 25 to 29.9 is considered overweight. A BMI of 30 or higher defines obesity.
- **Ethnic background**. Diabetes occurs more often in Hispanic/Latino Americans, African-Americans, Native Americans, Asian-Americans, Pacific Islanders, and Alaska natives.
- Hypertension, or high blood pressure, is a major risk factor for diabetes. Low levels of HDL "good" cholesterol and high triglyceride levels also are a risk factor for diabetes mellitus.
- **History of gestational diabetes**. Gestational diabetes during pregnancy gives a higher risk of developing T2DM.
- **Sedentary lifestyle**. Being inactive – exercising fewer than three times a week – increases the risk of developing T2DM.
- **Family history**. Having a family history of diabetes increases the risk of developing T2DM.
- **Polycystic ovary syndrome**. Women with polycystic ovary syndrome (PCOS) are at higher risk of T2DM.
- **Age**. As age increases, risk of developing T2DM also increases.

11. Pathophysiology of T2DM

11.1 Normal insulin action

In the fasting state 75% of total body glucose disposal takes place in non-insulin dependent tissue[5].In fact, brain glucose uptake occurs at the same rate during fed and fasting periods and is not altered in T2DM

The remaining 25% of glucose metabolism takes place in muscle, which depends on insulin. In the fasting state, approximately 85% of glucose production is derived from the liver. In the fed state, carbohydrate ingestion increases the plasma glucose concentration and stimulates insulin release form the pancreatic β cells. The resultant hyperinsulinemia will

1. Suppress hepatic glucose production.
2. Stimulate glucose uptake by peripheral tissues.

The majority (80-85%) of glucose that is taken up by peripheral tissues is disposed off in muscles, with only a small amount (4-5%) is being metabolized by adipocytes.

All the fat tissue is responsible for only a small amount of total body glucose disposal; it plays a very important role in the maintenance of total body glucose homeostasis. Small increments in the plasma insulin concentration exert a potential anti lipolytic effect, leading to a marked reduction in the plasma free fatty acids (FFA) levels. The decline in plasma FFA concentration results in the increased glucose uptake in muscle and reduces hepatic glucose production. Thus a decrease in the plasma FFA concentration lowers plasma glucose by both decreasing the production and enhancing the uptake in muscle.

T2DM individuals are characterized by

1. defects in insulin secretion and
2. Insulin resistance involved in muscle, liver, adipocytes.

Insulin resistance is present even in lean T2DM individuals.

11.2 Impaired insulin secretion

Impaired insulin secretion is also found in later stages of T2DM patients due to β cell dysfunction.

12. Treatment

Oral hypoglycemic drugs are used. They are classified as:

1. INSULIN SECRETAGOGUES
   - SULPHONYL UREAS - tolbutamide, chlorpropamide, glibencamide, glipizide, gliclazide, glimepiride
   - MEGLITINIDES - Repaglinide, Nateglinide
2. INSULIN SENSITIZERS
   - BIGUANIDES- metformin, phenformin
   - THIAZOLIDINEDIONE- rosiglitazone, pioglitazone
3. GLUCAGON LIKE PEPTIDE- exenatide
4. α - GLUCOSIDASE INHIBITORS- acarbose, miglitol

12.1 Insulin Secretagogues

12.1.1. Sulphonylureas:

Mechanism of Action: Sulphonylureas have direct effects on the insulin-producing islet β cells. The drugs bind to the β-cells sulphonylurea receptor (SUR) part of a transmembrance complex with adenosite tri 6.2 pottassium channels (K_{ATP} channels)[5,6] . Binding of the sulphonylurea closes these K_{ATP} channels; this reduces cellular potassium efflux favoring membrane depolarization. In turn depolarization opens voltage-dependent calcium channels, resulting in an influx of calcium leading to the release of insulin [fig 2]. When sulphonylureas interact with SURI in the β-cells plasma membrane they cause prompt release of pre-formed insulin granules adjacent to the plasma membrane the so called first phase of insulin release[7]. Sulphonylureas also increase the extended (second phase) of insulin release that involves the secretion of newly formed insulin granules. The increased release of insulin continues in the presence of sulphonylurea provided the β cells are fully functional.

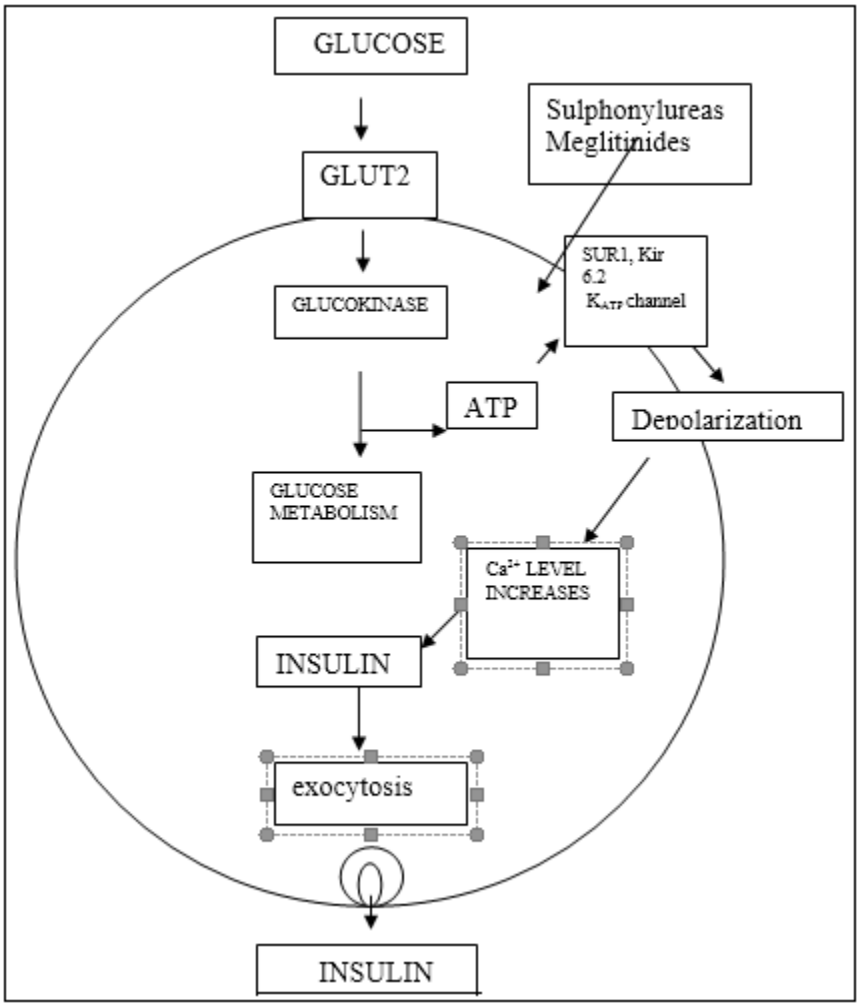

Fig 2: the insulin releasing effect of sulphonylureas and other agents on the pancreatic islet β- cells [8]

- **Adverse Effects**:

Hypoglycemia, which may be life threatening, is the most common and potentially most serious adverse effect[9]. Hypersensitivity reactions such as skin rashes, fever, erythema multiform, jaundice and blood dyscrasias are very rare. In some it precipitates acute porphyria in predisposed individuals. In contrast, glibenclamide shows a mild diuretic action. Weight gain is the common side effects of sulphonylureas. It must be kept minimum in patients with overt coronary heart disease [10].

- **Indications:**

Sulphonylureas remains a popular choice as first line oral therapy for patients with type 2 diabetes. Customarily they are preferred for patients who are not overweight since weight gain is usually promoted by their use. Sulphonylurea can be used in combination with agents from other classes of anti-diabetic agents, with the exception of other insulin secretagogues. Daytime sulphonylurea treatment may be used in combination with bedtime insulin, and can reduce insulin dose. Continued gradual loss of β-cells function is to be expected in most patients; this required escalating insulin doses with increasing duration of diabetes. Sulphonylureas should be introduced at a low dose, because of the consequences of hypoglycemia, especially in elderly patients.

12.1.2. Meglitinides:

Derivatives of meglitinide, such as repaglinide and nateglinide act as prandial glucose regulators. The prompt physiological rise in plasma insulin in response to meals is attenuated and its peak delayed. An initial surge of insulin release appears to be particularly important for effective post prandial suppression of hepatic glucose production and exacerbates postprandial hyperglycemia.

Because post prandial hyperglycemia contributes to elevated HbA_{1c} levels it is a logical therapeutic target [11, 12].

- **Mechanism of action**:

Benzamido prandial insulin releasers bind to the SUR1 in the plasma membrane of the β cell at a site distinct from the Sulphonylurea binding site. Since the K_{ATP} channel is closed when either the benzamido binding site or the Sulphonylurea binding site on the SUR1 is bound with its respective agonist, there is no advantage in giving a prandial insulin releaser in addition to sulphonylurea. However, drugs are in development that promote β cell proinsulin synthesis and act via signaling pathways distinct from the K_{ATP} channel [fig 2]. The short half-life of repaglinide results in enhancement of the first phase and early second phase of insulin secretion that is less sustained than that observed with sulphonylureas [13, 15].

- **Adverse effects**:

The overall incidence of hypoglycemic episodes is lower with meglitinides than with sulphonylureas. Sensitivity reactions usually transient can occur. A small increase in body weight can be expected in patients starting repaglinide as initial monotherapy. Nateglinide appears to have little effect on body weight when combined with metformin [18].

12.1.3 Insulin Sensitisers:

Insulin resistance is a prominent metabolic defect in most patients with type 2 diabetes[14, 15, and 16. Biguanides and thiazolidinediones act directly against insulin resistance and so are regarded as insulin sensitizing drugs.

- **Biguanides**:

The finding that *Galega officinalis* (god's rue or French lilac), historically used as a traditional treatment for diabetes in Europe, was rich in guanidine led to the introduction of several glucose- lowering guanidine derivatives such as metformin ,phenformin and buformin.

- **Mechanism of action**:

Metformin has a variety of metabolic effects. At the cellular level, metformin improves insulin sensitivity to some extent, an action mediated via post- receptor signaling pathways for insulin [17, 18]. Recent data has suggested that adenosine 5'-monophosphate-activator protein kinase (AMPK) is a possible intracellular target of metformin [19]. Through phosphorylation of key proteins,AMPK acts as a regulator of glucose and lipid metabolism and cellular energy regulation[20]. Since metformin lowers blood glucose concentrations without causing overt hypoglycemia [21]. The predominant glucose-lowering mechanism of action of metformin acts by reducing excessive rates of hepatic glucose production.

It reduces gluconeogenesis by increasing hepatic sensitivity to insulin and decreasing the hepatic extraction of certain gluconeogenic substrates. Hepatic glycogenolysis is also decreased by metformin. Insulin-stimulated glucose uptake in skeletal muscle is enhanced by metformin .This involves an increase in the movement of insulin-sensitive glucose transporters molecules to the cell membrane; an increase in the activity of the enzyme glycogens synthase which promotes the synthesis of glycogen. Metformin also acts in an insulin-independent manner to suppress the oxidation of fatty acids and to reduce tri glyceride levels in patients with hypertriglyceridaemia [22]. This reduces the energy supplying for hepatic gluconeogenesis and has favorable effects on glucose-fatty acids (Randle cycle in which fatty acids are held to compete with glucose as a cellular energy source) [21]. Glucose metabolism in the splanchnic bed is increased by metformin through insulin-independent mechanism. This may contribute to the blood glucose-lowering effect of the drug, and in turn may help to prevent

gains in body weight. Collectively, the cellular effects of metformin serve to counter insulin resistance and to reduce toxic metabolic effects of hyperglycemia (glucose toxicity) and fatty acids (lipotoxicity) in T2DM.

Metabolic and vascular effects of metformin

1 .Anti-hyperglycemic action
- Suppresses hepatic glucose output.
- Increases insulin mediated glucose utilization
- Decreases fatty acid oxidation
- Increases splanchnic glucose turnover

2. Weight stabilization or reduction
3. Improves lipid profile
- Reduces hypertriglyceridaemia
- Lowers plasma fatty acids and LDL-cholesterol; raises HDL –cholesterol in some patients.

4. No risk of serious hypoglycemia
5. Counters insulin resistance
- Decreases endogenous or exogenous insulin requirements
- Reduces basal plasma insulin concentrations

6. Vascular effects
- Increased fibrinolysis
- Improved endothelial function.

- **Adverse effects:**

It causes gastrointestinal effects including abdominal discomfort, diarrhoea. It also produces lactic acidosis renal insufficiency [23]. Hyperlactataemia occurs in cardiogenic shock and other illness that decrease tissue perfusion[24].

- **Indications:**

Metformin is the therapy of choice for overweight and obese patients with type2 diabetes [24]. It can be equally effective in normal weight patients. Metformin can also be used in combination with any other class of oral anti-diabetic agents or with insulin. Metformin alone is unlikely to cause serious hypoglycaemia, but hypoglycaemia becomes an issue when metformin is used in combination with an insulin-releasing agent or insulin. Metformin should be taken with meals or immediately before meals to minimise possible gastrointestinal adverse effects. The improvement in insulin sensitivity can cause ovulation to resume in cases of an ovulatory polycystic ovary syndrome (PCOS) [25]. The drug is contraindicated in patients with impaired renal function. Cardiac or respiratory insufficiency, or any other condition predisposing to hypoxia or reduced perfusion are further contraindications. Liver disease, alcohol abuse and a history of metabolic acidosis.

12.1.4 Thiazolidinediones

They improve whole body insulin sensitivity via multiple actions on gene regulation. They stimulate the nuclear receptor peroxisome proliferator-activator receptor (PPAR-γ), for which thiazolidinediones are potent synthetic agonists [26].

- **Mechanism of action**:

Stimulation of PPAR-γ is regarded as the principle mechanism through which thiazolidine diones enhance insulin sensitivity. PPAR-γ is expressed at highest level in adipose tissue, and less in muscle and liver. PPAR-γ operates in association with retinoid x-receptor. The resulting hetero dimer binds to nuclear response elements thereby modulating transcription of a range of insulin-sensitive genes, in the presence of necessary co factors [27, 35]. Reductions in plasma insulin concentrations and lowering of circulating triglycerides are additional indirect mechanism that may help to improve whole body insulin sensitivity. These drugs, like metformin require the presence of sufficient insulin to generate a significant blood glucose lowering effect.

- **Adverse effects:**

The adverse effects include heart disease, cardiac failure, oedema, anaemia, and hypoglycaemia. PPAR-γ activation in macrophages can reduce the production of some inflammatory cytokines and might increase transformation of monocytes to macrophages in the vascular wall.

- **Indications**: They are used as a monotherapy in obese and non- obese patients. They can also be used in combination with other oral hypoglycemic drugs and insulin. The

combination of thiazolidinediones and insulin can improve the glycemic control while reducing insulin dosage in obese patients [28].

12.1.5 GLP:

Glucagon-like peptide 1 (GLP-1) is produced by the proglucagon gene in L-cells of the small intestine in response to nutrients. It stimulates glucose-dependent insulin release from the pancreatic islets. In addition to its insulinotropic effects, it is thought to exert antihyperglycemic effects by slowing gastric emptying, inhibiting inappropriate glucagon release, stimulating β-cell proliferation and differentiation, and improving satiety.

- **Mechanism of action**:

It is a potent antihyperglycemic hormone, inducing glucose-dependent stimulation of insulin secretion while suppressing glucagon secretion. Such glucose-dependent action is particularly attractive because, when the plasma glucose concentration is in the normal fasting range, GLP-1 no longer stimulates insulin to cause hypoglycemia. GLP-1 appears to restore the glucose sensitivity of pancreatic β-cells, with the mechanism possibly involving the increased expression of GLUT2 and glucokinase. GLP-1 is also known to inhibit pancreatic β-cell apoptosis and stimulate the proliferation and differentiation of insulin-secreting β-cells. In addition, GLP-1 inhibits gastric secretion and motility. This delays and protracts carbohydrate absorption and contributes to a satiating effect.

- **Adverse effects**:

The most frequent adverse effects are hypoglycemia and gastrointestinal adverse events (nausea, diarrhea, and vomiting) [29].

12.1.6 α Glucosidase inhibitors:

Inhibitors of intestinal alpha glucosidase enzymes prevent the rate of carbohydrate digestion, thereby reduces the blood glucose level [30].

- **Mechanism of action**:

The alpha glucosidase inhibitors competitively inhibit the activity of alpha glucosidase enzymes in the brush border of enterocytes lining the intestinal villi. High affinity binding prevents these enzymes from cleaving their normal di-saccharide and oligo saccharide substrates into mono saccharides prior to absorption. This differs the completion of carbohydrate digestion until further along the intestinal tract, in turn se absorption to be delayed. The alpha glucosidase inhibitors should be taken with meals containing digestible carbohydrates not monosaccharides; these drugs generally do not significantly affect the absorption of glucose [30].

- **Adverse effects**:

The most common adverse effect of alpha glucosidase inhibitors are gastro intestinal disturbances. If the dosage is too high, undigested oligosaccharides pass into the large bowel [39]. Carbohydrates fermented by the flora of the large bowel cause flatulence, abdominal discomfort and sometimes diarrhea.

Hypoglycemia occurs only when an alpha glusodiase inhibitor is used in combination with a Sulphonylureas or insulin [31].

13. Complications

13.1 Acute complication:

- Hypoglycemia
- Ketoacidosis

13.2 Long term complications:

13.2.1 Macro vascular diseases:

- Damage to blood vessels may lead to cardiovascular diseases such as ischemic heart disease, myocardial infarction, and stroke [37].

13.2.2 Micro vascular diseases:

- erectile dysfunction
- Poor healing of wounds
- Diabetic retinopathy
- Diabetic nephropathy
- Diabetic neuropathy

Diabetes related foot problems [diabetic foot ulcers] [32].

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